REMARKS

I. Status of the Claims

Claims 1-22 and 25-33 are under examination, claims 14-22 having been withdrawn from consideration. Claims 1-13 and 25-33 are rejected under 35 U.S.C. §112, first and second paragraphs. The Examiner has maintained his rejection of claims 1-13 and 25-33 under 35 U.S.C. §103(a).

II. Rejection Under 35 U.S.C. §112, Second Paragraph

Claim 1 and dependent claims 2-13 and 25-33 are rejected under 35 U.S.C. §112, second paragraph, for allegedly being indefinite and failing to distinctly claim the subject matter of the invention. Office Action at pages 2-3. Specifically, the Examiner alleges that claim 1 is confusing because it recites "at least one binding region" (lines 1-2) and also that "the antigen binding region has a bivalent or multivalent structure." Claim 1 has been amended to recite "two or more binding regions," as suggested by the Examiner. Thus, Applicants request that the rejection be withdrawn.

III. Rejection Under 35 U.S.C. §112, First Paragraph

(1) The Examiner rejected claim 5 under 35 U.S.C. §112, first paragraph, for allegedly failing to be enabled by virtue of "the 24-25 kDa glycoprotein defined by Mab L6." Office Action at page 3. Applicants contend that this antibody was publicly available at the time the application was filed, as disclosed in Hellström *et al.*, Proc. Natl. Acad. Sci., Vol. 83:7059 (1986), and Hellström et al., Cancer Res, Vol. 46, No. 8, pp. 3917-23 (1986).

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(2) The Examiner also rejected claims 1-13 and 25-33 under §112, first paragraph, because the specification, while being enabled for claims reciting specific linkers, allegedly does not reasonably provide enablement for claims encompassing any and all linkers. Office Action at page 4. The Examiner alleges that Applicants' previous argument against the §103 rejection of Bosslet and Seemann in view of Huston, in which linkers internal to the sFv were discussed in order to support an argument for non-combination of the references, somehow casts doubt on what linkers are claimed. Therefore, the Examiner has requested Applicants to clarify the type of linkers that are recited in the claimed invention.

A review of the claims reveals that claims 1 and 8 refer to the link between the coding region of the sFv domain and the enzyme. Linkers internal to the sFv region are not recited in the claims. Claim 1 refers to two or more antigen binding regions "linked" to at least one prodrug activating enzyme. Claim 8 specifies that the link occurs via a peptide linker and the specification at page 4, last paragraph, discusses such linkage in more detail.

Applicants contend that the specification provides sufficient direction for one to design appropriate linkers between the antigen binding region and the enzyme. The specification states that an appropriate linker could be a "hinge region of an antibody or a hinge-like amino-acid sequence." Page 4, lines 26-30. Example 3 teaches a method for cloning a sFv region into a vector containing the huβ-glucuronidase gene and discloses the specific vectors that would incorporate a specific linker between coding

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regions of the sFv region and the enzyme. Page 13. Seq ID NO:1 codes for a humanized sFv fragment against CEA linked to a human glucuronidase gene.

IV. Rejections under 35 U.S.C. §103(a)

The Examiner has maintained his obviousness rejection of claims 1-9, 25-27, 30, and 33 over Bosslet *et al.* (Brit. J. Cancer, 1992) or Seemann *et al.* (EP 501,215) in view of Huston *et al.* (U.S. Pat. No. 5,132,405), and as necessary, Bosslet *et al.* (5,591,828) and Eaton *et al.* (EP 392,745). Office Action, pages 4-7.

He also rejected claims 1, 11-12, and 31-32 over these references, further in view of Ong *et al.* (Cancer Res., 1991), Bagshawe *et al.* (WO 89/10140), and Huston *et al.* (Methods Enzym., 1991). Claims 1, 10, 13, and 29 are rejected under the above-mentioned references, further in light of Goochee *et al.* (Biotechnol., 1991).

Claim 1 is common to all three rejections, and as all the remaining claims are dependent on claim 1, a showing that the primary references, the Bosslet paper or Seemann, together with the Huston patent, do not make constitute a *prima facie* case of obviousness, should be sufficient to show that the pending claims are not obvious over all of the references cited.

The Examiner contends that Bosslet and Seemann have essentially the same disclosure, showing a fusion protein comprising a Fab, a linker, and a human β-glucuronidase. Office Action at page 4. The Examiner acknowledges that the instant invention, which is constructed from a single polypeptide sFv construct, differs from the Fab constructs disclosed Bosslet and Seemann. He argues that one of ordinary skill in the art would have arrived at the instant invention by substituting the Fab disclosed in

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Bosslet and Seemann with a single chain antigen binding peptide as described in Huston. Office Action at page 5.

The Examiner contends that one would be motivated to make this substitution because the Fab constructs of Bosslet and Seemann are allegedly known to be functional equivalents of the single polypeptide sFv construct in the art of immunochemistry, as purportedly evidenced by the example in Huston's patent in col. 19. Office Action at page 5. The Examiner also argues that sFv constructs have certain advantages that would have motivated people to use them instead of Fab constructs. These advantages allegedly include increased stability, increased affinity, and the need to only introduce one construct into a cell instead of two. Office Action at pages 4-6.

The primary references do not render the claimed invention obvious:

Applicants' invention discloses a single stranded construct comprising two or more antigen binding regions and one or more constant regions linked to at least one prodrug-activating enzyme.

Neither the primary references, the Bosslet paper or Seemann, in combination with the secondary reference, the Huston patent, teach such a construct. Bosslet and Seemann refer to a Fab, comprising two polypeptide chains, linked to human β-glucuronidase, which consists of a single polypeptide chain. Conversely, while Huston teaches a construct with single stranded antigen binding regions, the reference only mentions enzymes in general, and does not specify that the translated enzyme is single stranded. This deficiency is not trivial. There are at least thousands of enzymes which consist of more than a single polypeptide chain. Furthermore, Huston provides a

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method for producing an Fv "preferably free of constant regions." Huston at col. 3, lines 39-40.

The Examiner has argued that one of ordinary skill in the art would remedy the shortcoming of Bosslet and Seemann, namely the use of a double-stranded Fab construct, by replacing the Fab with the sFv fragment of Huston. Office Action at page 4. He suggests that the Fab and sFv fragments of Bosslet, Seemann, and Huston are functional equivalents and could be used interchangeably, as evidenced in Huston at col. 19, lines 9-30. Office Action at page 5. This experiment shows that the binding regions are essentially the same for a Fv fragment as for a native protein.

However, while these data of Huston simply show and compare the binding of one set of antibodies *in vitro*, they do not show transcription of the linked enzyme or its subsequent activity on a prodrug. In contrast, Applicants show a much more sophisticated *in vitro* experiment (*see* Example 5, specification at page 16). In this experiment, the sFv-huβ-Gluc fusion protein is shown to bind to a CEA epitope, the enzyme is simultaneously expressed, and the enzymatic activity of the β-glucuronidase is measured using a specificity enzyme activity test (EP-A2-0 501 215). The test shows liberation of 4-methylumbelliferone from the prodrug 4-methylembelliferyl β-glucuronide.

In addition, the instant invention discloses a procedure for treating tumors with the sFv-enzyme construct *in vivo* (*see* Example 7, specification at page 18). This protocol can be used to treat mice with a subcutaneous tumors and subsequently analyze their plasma with immunological tests. Thus, even if, *arguendo,* one would be motivated to replace the Fab construct of Bosslet and Seemann with the sFv construct of Huston, their data only shows that a certain sFv may bind an antigen to a similar

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degree as a native protein, and, they presume, a Fab. It is only in the instant invention where the data is shown that a single stranded construct comprising two or more antigen binding regions and one or more constant regions can bind to a tumor antigen and transcribe a prodrug-activating enzyme. This unexpected result of the instant invention is simply not found in the prior art.

Finally, it is important to note that the sFv of Huston is an anti-digoxin antibody, rather than an antibody to a tumor antigen, as taught by the instant invention. Huston at column 5, lines 40-41. It is well known in the art it is notoriously hard to develop and work with antibodies to tumor antigens. *See* Janeway and Towers, Immunobiology, Garland Publishing, New York (1994), pages 12:33-12:36. First, many tumor antigens are actually peptides bound to MHC class 1 proteins, and it is very difficult to raise antibodies against such targets. Second, treatment with antibodies to tumor antigens often selects variants that have mutated the epitope recognized by the antibody, so that the antibody is ineffective against the subset of tumor cells. Thus, by targeting tumor antigens, Applicants have introduced an added level of complexity to the invention over that of Huston. Furthermore, this complexity shows the unexpected success of the instant invention.

Seemann and Bosslet teach away from the claimed invention:

Seemann specifically teaches away from the claimed invention, contending that that the antibody construct should be made in a way to "obtain a huTuMAb portion which is similar as possible to the original TuMAb in the binding properties." Seemann at Page 4, lines 4-6. This, teaching would lead one to use an antibody fragment such as a Fab, which has at least a portion of two strands of the light and heavy chains of the

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antibody attached by disulfide bonds in their native position, thus maintaining the three-dimentional structure of the antigen binding region. The reference would teach away from using a fragment such as the sFv used in the instant invention, which is single stranded.

The Examiner has admitted on the record that "(t)he Bosslet et al. and Seemann et al. references have essentially the same disclosure." Office Action at page 4. Furthermore, four of the six authors on the Bosslet paper are authors on the Seemann patent. Thus, it is likely the authors of the Bosslet article shared the view that it is desirable to obtain an antibody construct similar to the native antibody, and hence, chose the Fab construct.

Despite Seemann's words of caution against using antibody constructs that vary greatly from native antibodies, Applicants have shown that the an antibody-enzyme fusion protein can indeed be functional when it comprises an antibody fragment such as an sFv. In Example 5, Applicants show that the sFv-huβ-Gluc fusion protein can bind to a CEA epitope, simultaneously express an enzyme, and release a drug from a prodrug. Specification at page 16. This shows the novelty and unexpected success of the instant invention.

Huston teaches away from the instant invention:

Huston discloses sFv constructs that do not comprise a constant domain, in contrast to those taught in the instant invention. "The invention provides a method for producing intact biosynthetic antibody binding sites or native Fv free of all or substantially all constant region amino acids." Huston at col 4, lines 66-68 to col. 5, line

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1. In fact, Huston teaches away from using constant regions, saying that they "are not required for antigen recognition or binding" and that the antibody should be "preferably free of constant regions." Huston at col. 2, lines 29-30 and col. 3, lines 39-40.

There is no motivation to combine Huston with Bosslet or Seemann:

Applicants contend that there is no motivation to combine the teachings of the Huston patent with either the Bosslet paper or Seemann. Even if the references disclosed each and every element of the instant invention, the mere fact that the references can be combined does not render the resulting combination obvious unless the art also suggests the desirability of the combination. M.P.E.P. § 2143.01, *citing In re Mills*, 16 U.S.P.Q.2d 1430 (Fed. Cir. 1990). Because the requisite motivation and desirability are found only in the instant specification, and not in the cited references, the Examiner's burden for establishing a *prima facie* case of obviousness has not been met.

Seemann and Huston contain language which would discourage one of skill in the art to combine the references. As discussed above, Seemann teaches that the antibody should be as close as possible to a native antibody, which would lead one to use an antibody fragment such as a Fab, which has at least a portion of both strands of the light and heavy chains of the native antibody, thus maintaining the three-dimensional structure of the antigen binding region. The reference would teach away from using a fragment such as the sFv disclosed by Huston since it is much less similar to a native antibody, being single stranded. Conversely, Huston teaches that "constant regions are not required for antigen recognition or binding" and that the antibody is

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"preferably free of constant regions." Huston at col. 2, lines 29-30 and col. 3, lines 39-40. This would discourage one from using antibodies disclosed in Seemann, since they contain constant domains (*see,* for example, claims 2-5)

Similarly, one would not be motivated to combine the Bosslet and Huston references because Bosslet, like Seemann, discloses a Fab, an antibody fragment that is closely related to a native antibody, in contrast to the more artificial sFv disclosed by Huston. Conversely, one would not be motivated to combine Huston with Bosslet because Huston teaches against using antibody fragments having constant regions, as mentioned above. Thus, antibodies disclosed in Bosslet would not be desirable, having "the C_H1 region of human IgG3." Bosslet at page 235.

Because there is no motivation to combine the Huston with either Bosslet or Seemann, and in fact, language against combining the references, Applicants request that the rejection be withdrawn.

The tertiary references fail to cure the deficiencies of Seemann, Bosslet, and Huston

Applicants contend that the tertiary references do not remedy the shortcomings of Seemann, the Bosslet paper, and Huston. Furthermore, the references themselves differ from the instant invention. The tertiary references include the Bosslet patent, Eaton, Ong, Bagshawe, and Goochee.

The Bosslet patent teaches a construct consisting of a Fab fragment, rather than a single stranded antibody such as that of the claimed invention. One would not be motivated to combine the reference with the sFv of Huston because Bosslet discloses a

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construct comprising a constant domain. *See*, for example, claim 1. Huston teaches away from using a constant region, as discussed above.

Eaton discloses certain prodrugs having β-lactamase action that can be used in immunoconjugates. However, Eaton teaches the hydrolysis of β-lactamate into various degredation products to form the active drug. The degradation products of Eaton are not precisely defined by structure, in contrast to the present inventive concept, wherein the prodrug is a biologically inactive compound transformed into an active compound by the precise enzymatic removal of functional groups.

The Examiner argues that Ong and Bagshawe teach that glycosylation of antigen binding regions permits rapid clearing, which would motivate one to rely on these references in arriving at the claimed invention. Office Action, pages 8-9. However, Ong differs from the instant invention in that they use full monoclonal antibodies, which are double stranded. Similarly, Bagshawe teaches clearance of $F(ab')_2$ fragments, which are also double stranded. In contrast, the instant invention teaches single standed constructs linked to an enzyme. Glycosylation of single stranded constructs is only taught in the instant invention. Furthermore, Bagshawe teaches the use of carboxypeptidase G2, a dimeric protein, in contrast to the single stranded enzyme taught by the instant invention.

The Examiner has argued that Goochee has shown that it was know that yeast could be used to express polypeptides having a high degree of mannosylation and having a high clearance rate. He contends that it would have been obvious to express the polypeptide of Claim 1 in yeast to provide clearance. Applicants contend that Goochee teaches away from using yeast cells for expressing mammalian proteins,

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saying that the differences in their respective oligosaccharide structures makes it "difficult to be enthusiastic about the use of yeast...as hosts for the production of human therapeutic glycoproteins." Goochee at page 1352, col. 2.

VII. Conclusion

Applicants respectfully request the entry and reconsideration of this amendment, placing pending claims 1-13 and 25-33 in condition for allowance. Applicants submit that the proposed amendment to claim 1 does not raise new issues or necessitate the undertaking of any additional search of the art by the Examiner, since all of the elements and their relationships were inherent in the claims as examined. Therefore, this Amendment should allow for immediate action by the Examiner.

Finally, Applicants submit that the entry of the amendment would place the application in better form for appeal, should the Examiner dispute the patentability of the pending claims.

In view of the foregoing remarks, Applicants submit that this claimed invention, as amended, is neither anticipated nor rendered obvious in view of the prior art references cited against this application. Applicants therefore request the entry of this Amendment, the Examiner's reconsideration and reexamination of the application, and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

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ADDENDUM

1. A compound comprising [at least one] two or more antigen binding [region] regions linked to at least one prodrug-activating enzyme, where the antigen binding [region(s) is composed of] regions comprise a single polypeptide chain, and where the compound has a bivalent or a multivalent structure.

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APPENDIX TO AMENDMENT OF JULY 12, 2002

Version with Markings to Show Changes Made

Amendments to the Claims

1. (Amended) A compound comprising two or more antigen binding regions linked to at least one prodrug-activating enzyme, **[**where**]** wherein

a) the antigen binding regions **[**comprise**]** consist of a single polypeptide chain**[**,**]** ;

b) the single polypeptide chain is comprised of a first variable domain, a second variable domain, and a polypeptide linker connecting the first variable domain and the second variable domain;

c) a nucleotide sequence encoding the polypeptide linker is formed by two partially overlapping PCR primers during a PCR reaction that links the first variable domain and the second variable domain; and **[**where**]** wherein

d) the compound has a bivalent or a multivalent structure.

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